

Claims:

1. Preparation for the application of agents in the form of minute droplets of fluid, in particular with a membrane-like coating consisting of one or several layers of amphiphilic molecules or of one amphiphilic carrier substance, for transporting agents into and through natural barriers and constrictions such as skin and similar materials, characterized by the fact that each preparation contains an edge active substance at a concentration which amounts up to 99 mol-% of the concentration of this substance required to solubilize the droplet.
2. Preparation according to claim 1, wherein the concentration of edge active substance amounts to at least 0.1 mol-%, in particular between 1 and 80 mol-%, preferably between 10 and 60 mol-%, and particularly preferred between 20 and 50 mol-% of the solubilization-inducing concentration of edge active substances, whereby the edge activity of a droplet unit is preferably close to approx. 10 Piconewton or less.
3. Preparation according to claims 1 or 2, characterized by the fact that the preparation contains an amount of an amphiphilic substance as a carrier or as a basis for the membrane-like envelope of the droplet forming hydrophilic fluid, the agent being contained in the carrier substance, in the shell, and/or in the droplet material itself.
4. Preparation as claimed in claim 3, wherein said amphiphilic substance is a lipid-like material and said edge active substance is preferably a surfactant.

5. Preparation as claimed in one of claims 1 through 4, wherein the content of said amphiphilic substance for the applications on human or animal skin amounts to 0.01 through 30 weight-% of the preparation mass, preferably between 0.1 and 15 weight-% and particularly preferred between 5 and 10 weight-%.
6. Preparation as claimed in one of claims 1 through 4, wherein the content of the amphiphilic substance in the formulation for application on plants is 0.000001 through 10 weight-%, preferably between 0.001 and 1 weight-% and particularly preferred between 0.01 and 0.1 weight-%.
7. Preparation as claimed in any one of the preceding claims, wherein an agent is an adrenocorticostatic, a  $\beta$ -adrenolytic, an androgen or antiandrogen, antiparasitic, anabolic, anaesthetic or analgesic, analeptic, antiallergic, antiarrhythmic, antiarterosclerotic, antiasthmatic and/or bronchospasmolytic, antibiotic, antidrepressant and/or antipsychotic, antidiabetic, an antidote, antiemetic, antiepileptic, antifibrinolytic, anticonvulsive, an anticholinergic, an enzyme, coenzyme or a corresponding inhibitor, an antihistaminic, antihypertonic, a biological inhibitor of drug activity, an antihypotonic, anticoagulant, antimycotic, antimyasthenic, an agent against Morbus Parkinson, an antiphlogistic, antipyretic, antirheumatic, antiseptic, a respiratory analeptic or a respiratory stimulant, a broncholytic, cardi tonic, chemotherapeutic, a coronary dilatator, a cytostatic, a diuretic, a ganglium-blocker, a glucocorticoid, an antiflow agent, a haemostatic, hypnotic, an immunoglobuline or its fragment or any other immunologically active substance, a bioactive carbohydrate (derivative), a contraceptive, an anti-migraine agent, a mineralcorticoid, a morphine-

antagonist, a muscle relaxant, a narcotic, a neuraltherapeutic, a nucleotide, a neuroleptic, a neurotransmitter or some of its antagonists, a peptide(derivative), an opthalmic, (para)-sympaticomimetic or (para)sympathicolytic, a protein(derivative), a psoriasis/neurodermitis drug, a mydriatic, a psychostimulant, rhinologic, any sleep-inducing agent or its antagonist, a sedating agent, a spasmolytic, tuberlostatic, urologic, a vasoconstrictor or vasodilatator, a virustatic or any wound-healing substance, or several such agents.

8. Preparation as claimed in one of claims 1 through 6, wherein said agent is a growth modulating substance for living organisms.
9. Preparation as claimed in one of claims 1 through 6, wherein said agent exerts some biocidal activity and particularly is an insecticide, a pesticide, a herbicide or a fungicide.
10. Preparation as claimed in one of claims 1 through 6, wherein an agent is an attractant, in particular from the class of pheromones.
11. A method for manufacturing preparations for the application of agents in the form of minute droplets of a fluid, in particular in a membrane-like 'envelope' consisting of one or several layers of amphiphilic molecules, or supplemented with an amphiphilic carrier substance, in particular for the transport of agents in and through natural barriers and constrictions, such as skin and the like, characterized by the fact that the concentration of an edge active substance required for the solubilization of a carrier entity is determined and

then an amount of the edge active substance which is close to the former concentration but still guarantees a sufficient carrier stability and permeation capability is used for the preparation.

12. Method as claimed in claim 11, wherein the stability and the permeation capacity of the fluid 'droplet' are determined by means of filtration, if required under pressure, through a fine-pore filter or by means of any other controlled mechanical fragmentation.
13. Method as claimed in claims 11 or 12, wherein the content of said edge active substance is between 0.1 and 99 mol-%, and in particular between 1 and 80 mol-%, preferably between 10 and 60 mol-% and most preferred between 20 and 50 mol-% of the concentration at which solubilization of the carrier is achieved.
14. Method as claimed in one of claims 11 through 13, wherein said mixture of substances required for the formation of a preparation is subjected to filtration, ultrasonication, stirring, agitating or any other mechanical fragmentation.
15. Preparation as claimed in one of claims 1 through 10, wherein said preparation for non-invasive application contains at least one antidiabetic agent, in particular insulin.
16. Preparation as claimed in claim 15, characterized by the fact that it contains a physiologically compatible polar or non-polar lipid as an amphiphilic carrier substance, the carrier membrane preferably having a double layer structure.

17. Preparation as claimed in claim 16, wherein the amphiphilic substance is a lipid or a lipoid from any biological source or a corresponding synthetic lipid, or else comprises a modification of such lipids, a glyceride, in particular glycerophospholipid, isoprenoidlipid, sphingolipid, steroid, sterin or sterol, a sulfur- or carbohydrate-containing lipid, or else any other lipid which forms stable double layers, preferably a half-protonated fluid fatty acid, and preferably a phosphatidylcholine, phosphatidylethanolamine, phosphatidylglycerol, phosphatidylinositol, a phosphatidic acid, a phosphatidylserin, a sphingomyelin or sphingophospholipid, glycosphingolipid (e.g. cerebroside, ceramidopolyhexoside, sulfatide, sphingoplasmalogene), a ganglioside or any other glycolipid or a synthetic lipid, preferably a dioleoyl-, dilinoleyl-, dilinolenyl-, dilinolenoyl-, diarachidoyl-, dimyristoyl-, dipalmitoyl, distearoyl, phospholipid or corresponding sphingosinderivative, a glycolipid or any other diacyl- or dialkyl-lipid.
18. Preparation as claimed in one of claims 15 through 17, containing several edge active substances.
19. Preparation as claimed in one of claims 15 through 18, wherein said edge active substance is a nonionic, a zwitterionic, an anionic or a cationic surfactant, in particular a long-chain fatty acid or a long-chain fatty alcohol, an alkyl-trimethyl-ammonium-salt, alkylsulfate-salt, cholate-, deoxycholate-, glycodeoxycholate-, taurodeoxycholate-salt, dodecyl- dimethyl-aminoxide, decanoyl- or dodecanoyl-N- methylglucamide (MEGA 10, MEGA 12), N-dodecyl-N,N- dimethylglycine, 3-

(hexadecyldimethylammonio)-propane-sulfonate, N-hexadecyl-sulfobetaine, nonaethylene-glycol-octylphenylether, nonaethylene-dodecylether, octaethyleneglycol-isotridecylether, octaethylene-dodecylether, polyethylene glycol-20-sorbitane-monolaurate (Tween 20), polyethylene glycol-20-sorbitane-monooleate (Tween 80), polyhydroxyethylene-cetylstearyl ether (Cetomacrogol, Cremophor O, Eumulgin, C 1000) polyhydroxyethylene-4-laurylether (Brij 30), polyhydroxyethylene-23-laurylether (Brij 35), polyhydroxyethylene-8-stearate (Myrj 45, Cremophor AP), polyhydroxyethylene-40-stearate (Myrj 52), polyhydroxyethylene-100-stearate (Myrj 59), polyethoxylated castor oil 40 (Cremophor EL), polyethoxylated hydrated castor oil, sorbitane-monolaurate (Arlacel 20, Span 20), particularly preferred decanoyl- or dodecanoyl-N-methylglucamide, lauryl- or oleoylsulfate-salts, sodiumdeoxycholate, sodiumglycodeoxycholate, sodiumoleate, sodiumelaidate, sodiumlinoleate, sodiumlaurate, nonaethylene-dodecylether, polyethylene glycol-20-sorbitane-monooleate (Tween 80), polyhydroxyethylene-23-laurylether (Brij 35), polyhydroxyethylene-40-stearate (Myrj 52) and/or sorbitane-monolaurate (Arlacel 20, Span 20) and lysophospholipid, such as n-octadecylen(=oleoyl)-glycerophosphatidic acid, -phosphorylglycerol, or -phosphorylserine, n-dilauryl-glycerophosphatidic acid, -phosphorylglycerol, or -phosphorylserine, n-tetradecyl-glycerophosphatidic acid, -phosphorylglycerol, or -phosphorylserine and corresponding palmitoeloyl-, elaidoyl-, vaccenyl-lysophospholipids.

20. Preparation as claimed in one of claims 15 through 19, characterized by the fact that it contains 1 through 500 I.U. insulin/ml as agent, preferably between 20 and 100

I.U. insulin/ml and the concentration of the carrier substance in the preparation is in the range of 0.1 through 20 weight-%, in particular between 0.5 and 15 weight-%, particularly preferred between 2.5 and 10 weight-%.

21. Preparation as claimed in one of claims 15 through 20, characterized by the fact that a phosphatidylcholine and/or a phosphatidylglycol is used as an amphiphilic substance, and that a lysophosphatidic acid or lysophosphoglycerol, a deoxycholate-, glycodeoxycholate- or cholate salt, a laurate, myristate, oleate, palmitoleate, or a corresponding phosphate- or sulfate-salt, and/or a Tween- or a Myrj-surfactant is used as an edge active substance, recombinant human insulin being the preferred agent.
22. Preparation as claimed in one of claims 15 through 21, wherein the radius of said vesicular droplets in a preparation is between approx. 50 and approx. 200 nm, preferably between approx. 100 and 180 nm.
23. A method for the preparation of a formulation for the non-invasive application of antidiabetic agents, wherein said liposome-like droplets are formed from at least one amphiphilic substance, at least one hydrophilic fluid, at least one edge active substance, and at least one antidiabetic agent which together form the preparation.
24. Method as claimed in claim 23, wherein the edge active substance and the amphiphilic substance, and the hydrophilic substance and the agent are separately mixed together and, if required, dissolved in a solution, the resulting mixtures or solutions then being combined

as one mixture to induce the formation of carrier particles, particularly by action of mechanical energy.

25. Method as claimed in claims 23 or 24, wherein said amphiphilic substance is either used as such or dissolved in a physiologically compatible solvent which is very frequently miscible with hydrophilic fluids, in particular water, or in a solvation mediating agent together with a polar solution.
26. Method as claimed in claim 25, wherein the polar solution contains at least one edge active substance.
27. Method as claimed in one of claims 23 through 26, characterized by the fact that the formation of droplets is induced by substance addition into a fluid phase, evaporation from a reverse phase, using an injection- or dialysis procedure, with the aid of mechanical stress such as shaking, stirring, homogenizing, ultrasonication, shear, freezing and thawing, or high- or low-pressure filtration.
28. Method as claimed in claim 27, characterized by the fact that the formation of droplets is caused by filtration the filtering material having pore diameters of 0.1 through 0.8  $\mu\text{m}$ , in particular with 0.15 through 0.3  $\mu\text{m}$ , especially preferred 0.22  $\mu\text{m}$ , several filters being sometimes used in a sequence.
29. Method as claimed in one of claims 23 through 28, wherein inclusion of said agents occurs at least partly after the droplet formation.
30. Method as claimed in one of claims 23 through 29, wherein liposome-like droplets are prepared just before



their application from a suitable concentrate or a lyophilisate.

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